Atypical Antipsychotics

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Atypical antipsychotics are a major therapeutic advance for the treatment of schizophrenia and other related psychotic disorders. These agents improve quality of life and medication compliance, as well as decrease suicidal tendencies and depression in these patients. Over the past decade, their off-label and adjunctive usage has expanded to other psychiatric disorders, such as acute mania, psychotic depression, severe agitation, dementia-related psychosis and behavioural disturbance. Atypical antipsychotics have also been used to treat borderline personality disorder, substance dependence disorders, treatment-refractory obsessive-compulsive disorder and depression.[1-5]

While atypical antipsychotics have a significantly reduced potential to induce acute extrapyramidal symptoms (EPS) and tardive dyskinesia, there is growing concern among health-care professionals regarding their side-effect profile.[6,7] These concerns primarily involve metabolic side effects, consisting of excessive weight gain, abnormal glucose regulation and dyslipidemia, as well as their consequent iatrogenic morbidity.[8-10] In the past three years alone, there has been a surge of published data, often extracted from large multicentre-controlled clinical

trials of atypical antipsychotics. The results not only confirm the therapeutic efficacy of atypical antipsychotics, but also demonstrate clinically relevant differences in their side-effect profiles.

This article will focus on new research in the area of atypical antipsychotic-induced weight gain and offer practical strategies for clinicians to use in management and prevention.

Canada's overweight and obesity epidemic

Obesity surveillance maps from 1985 to 1998, showing the prevalence of obesity in Canada, has more than doubled from 5.6% to 14.8%, with sharp increases also reported in the U.S. (increase from 12% in 1991 to 17.9% in 1998).[11] Obese and overweight individuals, defined according to Body Mass Index (BMI) values by the World Health Organization, have a high prevalence of comorbid illnesses and increased mortality (Tables 1 and 2).[12,13]

Schizophrenia and other mental disorders

It is well known that individuals with schizophrenia and other chronic mental disorders often smoke and abuse alcohol, which increase the risk of obesity-related illnesses. Poor dietary habits, lack of exercise, residual negative symptoms, increased inactivity with each in-patient admission, social isolation, low socioeconomic status and other barriers make it difficult for a schizophrenic individual to maintain a normal BMI.

Women with schizophrenia have a significantly higher mean BMI than do women without the disorder, and in general, people with schizophrenia show an equal, or greater, degree of obesity than non-schizophrenics.[14] A recent controlled study found obesity in bipolar disorder patients to be significantly more prevalent as compared to a matched general population sample.[15] In this population, obesity was found to be associated significantly with antipsychotic drug treatment, but not with lithium treatment.[16]

Differential weight gain liability

Weight gain is a common side effect of conventional antipsychotic drugs. The weight gain observed with several atypical antipsychotics is often greater than that reported with conventional antipsychotics. The notion that weight gain is correlated with antipsychotic drug response was suggested as early as 1959. In 2002, the same contention made with atypical

Summary

Antipsychotics and Weight Gain

- One should not determine drug selection of an atypical antipsychotic strictly on the basis of weight gain or other metabolic side effects.
- Although regrouped under a common nomenclature, differences exist among atypical antipsychotics, especially with regard to the metabolic side-effect profiles. These differences need to be taken into account when choosing which atypical antipsychotic to prescribe.

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Table 1

Weight Status According to BMI (kg/m^2) Values

Weight status	BMI (kg/m^2)
Underweight	< 18.5
Normal	18.5 to 24.9
Overweight	25.0 to 29.9
Obesity	≥ 30

BMI = body mass index

antipsychotics remains the subject of much debate. This notion, however, is reminiscent of another earlier, and ultimately false, assumption that held that with a "neuroleptic", induction of EPS was required to achieve therapeutic effect.

Table 3 provides mean weight gain estimates following short-term (10 weeks) treatment with antipsychotics. These data are derived from two sources — a comprehensive meta-analysis by Allison *et al.* and a study by Rak *et al.*, which reported on weight changes during quetiapine therapy.[17,18] Weight gain changes often continue past this initial short-term treatment period, however, and these results are not indicative of long-term weight gain, which can be considerably higher.

Evidence attesting to the complexity of weight change with atypical antipsychotic treatment is provided by an analysis of long-term weight change in 178 patients with schizophrenia who participated in controlled and open-label extension trials of quetiapine monotherapy for at least six months.[19] The mean treatment duration was 18.6 months, with a reported mean daily dose of 473 mg. An overall weight-neutral effect was reported with a tendency for quetiapine to exert a "normalizing" effect in underweight and obese patients.

Clozapine remains the most effective antipsychotic for treatment-refractory patients with schizophrenia in spite of concerns for its significant metabolic side-effects.[20,21] There is some speculation that clozapine can halt illness progression. This is due, in part, to its demonstrated ability to improve cognitive function in patients with schizophrenia. This has lead to the suggestion that clozapine be used as a first-line agent in patients with first-break psychosis. Various degrees of cognitive improvement, however, also have been reported in patients treated with other atypical antipsychotics. At this time it is too early to know if this potential advantage in this subgroup of patients outweighs clozapine's considerable side-effect risk.

In a recent study, 157 in-patients with chronic schizophrenia or schizoaffective disorder and a history of suboptimal treatment response were randomly assigned to treatment with clozapine, olanzapine, risperidone or haloperidol over a 14-week period.[22] The reported average weight gains were 4.2 kg, 5.4 kg, 2.3 kg and 0.2 kg respectively. Although the authors recognized the antipsychotic doses employed in the study were high (mean dose levels for the last six weeks of the study were 526.6 mg/day for clozapine, 30.4 mg/day for olanzapine, 11.6 mg/day for risperidone and 25.7 mg/day for haloperidol), the results are consistent with previous findings that clozapine and olanzapine are associated with the greatest magnitude of weight gain.

The novel antipsychotic ziprasidone, released in the U.S. and in other parts of the world, is soon expected to receive regulatory approval in Canada. Its reported efficacy in large multicentre-controlled clinical trials in schizophrenia, with low incidence of EPS and prolactin elevation, antidepressant effects and its weight-neutral profile have attracted considerable attention. Ziprasidone is also suggested to have fewer effects on serum lipids and insulin resistance.[8,9] There are concerns, however, about ziprasidone's greater capacity to prolong the QT/QTc interval when compared to other antipsy-

Table 2

Comorbid Illnesses Associated With Overweight And Obesity

- Dyslipidemia
- Type II diabetes mellitus
- Gallstones
- Hypertension
- Coronary artery disease
- Congestive heart failure
- Stroke
- Osteoarthritis
- Cancer (endometrial, breast, colon)

Table 3

Estimated Mean Weight Gain after 10 Weeks of Antipsychotic Drug Treatment

Drug	Kg
• Haloperidol	1.08
• Risperidone	2.10
• Quetiapine	2.16
• Olanzapine	4.15
• Clozapine	4.45
• Ziprasidone	0.04

chotics.[23,24] Long-term studies with ziprasidone report a mean weight gain of 0.23 kg at six months, with 14% of patients gaining ≥ 7 % of their baseline weight at approximately one year.[8]

In summary, the magnitude of weight gain and its time course varies among atypical antipsychotics. Clozapine and olanzapine are associated with the largest effects on short- and longer-term weight gain. Risperidone has an intermediate effect on weight gain. Quetiapine imparts minimal to intermediate weight gain, depending on short- and longer-term treatment analyses. Ziprasidone appears to have the least effect on weight gain. Although weight gain generally tends to plateau over time, this period varies between atypicals. For clozapine and olanzapine, a weight gain plateau is reported to occur later (between 39 and 52 weeks of treatment), while this plateau is believed to occur earlier in the first few months of treatment with risperidone, quetiapine and ziprasidone.[8] Nonetheless, weight gain can extend over a period of years in some individuals.

Pharmacologic mechanisms

When initiating treatment with an atypical antipsychotic, the physician should assess the patient's individual and family history for obesity, dyslipidemia, diabetes and other obesity-related risk factors.

There is a strong correlation between histamine H_1 antagonist properties of atypical antipsychotics and weight gain. Serotonin 5-HT_{2C} antagonism is also believed to play a role in atypical antipsychotic-induced weight gain. Ziprasidone, which is associated with a weight-neutral profile, has, however, a strong *in vivo* affinity for the 5-HT_{2C} receptor.

Leptin, a protein and novel hormone, may play a key role in regulating body weight in humans. Increases in leptin levels have been reported to correlate with increases in body weight and BMI in clozapine and olanzapine treated patients with schizophrenia.[25]

Atypical antipsychotic drug selection

One should not determine drug selection of an atypical antipsychotic strictly on the basis of weight gain or other metabolic side effects. If this were the case, clozapine would not have been as widely used in treatment-refractory patients with schizophrenia, and thousands of these individuals would not have benefited from its life-altering therapeutic effects.

Although regrouped under a common nomencla-

ture, differences do exist among atypical antipsychotics, especially with regard to the metabolic side-effect profiles. These differences need to be taken into account when choosing which atypical antipsychotic to prescribe. Therapeutic efficacy is important, yet statistically significant differences in symptom improvement among atypical antipsychotics (with the exception of clozapine for treatment-refractory patients with schizophrenia) are subject to study design and post-hoc statistical bias. These biases often translate into relatively modest differences of limited clinical significance.

Deciding which atypical antipsychotic agent to prescribe should be done on a case-by-case basis, but rests on such issues as:

- Overall illness and symptom severity;
- Therapeutic efficacy and side-effect profile;
- Age;
- Personal and family history of obesity-related risk factors;
- Baseline weight, BMI, glucose and lipid levels;
- Prior sensitivity to EPS and weight gain with psychotropic agents;
- Medication compliance history; and
- Knowledge of the patient's threshold of tolerance

If there is significant weight gain and the patient's BMI shifts to the upper range of overweight or to obesity levels, a weight-reduction program combined with a pharmacological agent to counter further weight gain and promote weight loss should be initiated.

for weight gain.

Independent risk factors

Initial low BMI (< 23 kg/m^2) has been linked with greater weight gain, but results for this association have been inconsistent.[8,26] A strong correlation between antipsychotic dosage and weight gain in studies of one year or more has not been found. Nevertheless, a plateau effect of weight gain can confound this association, which has been reported in short-term studies.[8]

Mood stabilizers, such as lithium and valproate, are regularly used in combination with atypical antipsychotics. Such combination therapy poses the risk of significant accrued weight gain. A retrospective study by Meyer *et al.* reported a twofold increase in weight gain when lithium or valproate was added to risperidone, and an almost threefold increase with olanzapine.[8] For many patients, the benefits of this combination therapy outweigh this risk, but in an era of increasing polypharmacy, one should periodically re-evaluate its benefit-to-risk ratio.

Age effects are being increasingly recognized. Weight gain in older patients (≥ 60 years old) treated with atypical antipsychotics is lower than that seen in younger adults.[8]

Baseline work-up and monitoring

When initiating treatment with an atypical antipsychotic, the physician should assess the patient's individual and family history for obesity, dyslipidemia, diabetes and other obesity-related risk factors. Physicians should also obtain a baseline weight, BMI, fasting plasma glucose and serum lipid profile.

Furthermore, the patient should be informed of the risks and of other relevant side effects early on in treatment. If necessary, one can reassess the choice of the atypical antipsychotic and determine if pharmacological intervention to reduce or prevent any further weight gain is required. The physician also should inquire about physical activity and dietary habits. It is helpful to advise the sedentary patient to increase physical exercise with a daily brisk walk, to limit food and liquid intake of high caloric and poor nutritional value and to keep a record of food intake and weight change.

Monitoring weight gain and other side effects should be individually tailored and match with the agent's side-effect profile. Patients taking clozapine and olanzapine should ideally have their weight and BMI measured at baseline and subsequently on a monthly basis. Furthermore, their fasting plasma glucose and serum lipids should be measured quarterly throughout the first year of treatment and every six to 12 months thereafter, unless specific risk factors require more extensive follow-up. Other atypicals warrant less frequent monitoring, especially after the first three months of treatment. Following this initial period, and in the absence of excessive weight gain and abnormal laboratory results, subsequent measurements and laboratory testing usually can be conducted on an annual basis.

If a weight scale is not readily accessible to the clinician, which can occur even in hospital-based psychiatric outpatient settings, an acceptable alternative is to ask the patient to weigh him/herself on a monthly basis, chart the weight on a portable calendar or diary and bring it to each outpatient visit. If there is significant weight gain and the patient's BMI shifts to the upper range of overweight or to obesity levels, a weight reduction program combined with a pharmacological agent to counter further weight gain and promote weight loss should be initiated. One should also consider adding a weight-reducing pharmacological agent preventively in high-risk patients and in those with a particularly low threshold of tolerance for weight gain, who are likely to become noncompliant and relapse.

Medication non-compliance

Atypical antipsychotic-induced weight gain is asso-

ciated clearly with medication noncompliance.[17] Although drug discontinuation as a consequence of weight gain is uncommon in results of clinical trials with atypical antipsychotics, it is not a rare occurrence in clinical settings. Factors that most likely contribute to this difference are frequent study visits, greater patient-staff interaction and participants' motivation in the course of a clinical trial, which may lead them to be more tolerant of weight gain than their counterparts in the usual clinical setting.

Counteractive pharmacological agents

Topiramate is an anticonvulsant that may have antimanic and mood-stabilizing effects in bipolar disorder, but large controlled studies are needed to substantiate this claim. A frequent and dose-related side effect of topiramate is weight loss. This agent is being used to counter weight gain in bipolar, schizoaffective and schizophrenic patients treated with atypical antipsychotics. It is recommended to titrate the dose of topiramate slowly with 50 mg weekly increments. The usual dosage range varies between 100 mg/day and 300 mg/day. Side effects of topiramate include sedation, cognitive slowing and a 1.5% increased risk of kidney stones.

In a double-blind placebo-controlled study of 132 patients with schizophrenia, schizoaffective disorder and schizophreniform disorder, the H_2 antagonist nizatidine at a dose of 300 mg twice daily (bid) significantly reduced olanzapine-associated weight gain.[27] Patients receiving olanzapine and nizatidine had a mean weight gain of 2.76 kg, while the group on olanzapine and placebo had a mean weight gain of 5.51 kg. This preventive strategy is promising, but its potential efficacy to treat olanzapine and other atypical-antipsychotic-induced weight gain has not yet been established.

Orlistat, a gastric and pancreatic lipase inhibitor with no central nervous system or systemic activity, is used for obesity management, including weight loss and weight maintenance when used in conjunction with a calorie-reduced diet. It acts by inhibiting the absorption of about 30% of dietary fats. Frequent gastrointestinal (GI) side effects can be reduced with fibre supplementation. A double-blind placebo-controlled multicentre long-term treatment study for obesity showed a weight loss of 10.2% from baseline weight after one year of treatment with orlistat 120 mg three times daily (tid), as compared to 6.1% for placebo-treated patients.[13] After two years, fewer patients taking orlistat treatment regained weight when compared to the placebo group. In addition, positive effects on lipid levels and glucose tolerance were observed. In psychiatric patients, orlistat's beneficial effect and tolerability currently are limited to case reports.[28] Its lack of known drug interactions with psychotropic medications makes its use on the treatment of obese, chronically mentally ill patients receiving atypical antipsychotics worthy of further investigation.

A 12-week open-label pilot study in 19 children aged 10 to 18 years receiving metformin 500 mg tid showed significant weight and BMI reductions in 15 patients who were treated with olanzapine (with or without valproate), risperidone (with or without valproate), quetiapine monotherapy or valproate monotherapy.[29] Although the authors reported good tolerability, this weight loss effect of metformin will need to be replicated in a controlled setting.

Erratum

Three references in the article "Communication in Health Care" (*The Canadian Journal of CME*, June 2002) were incomplete and should have read as follows:

10. Winkelaar P: The importance of interspeciality communication. CMPA Information Letter 2000; 15(1):1.
11. Winkelaar P: When joking isn't funny. CMPA Information Letter 1999; 14(1):1.
12. Gambhir IB: Reducing your risk when you're not available. CMPA Information Letter 2000; 15(2):1.

We regret the error.

Conclusion

Losing weight is very hard to achieve for most people in the general population. Weight control is, therefore, even more challenging for psychiatric patients, especially those with chronic mental disorders such as schizophrenia. Behavioural intervention with a weight reduction program is often extremely difficult in this patient population. Preventing weight gain in this already at-risk population is the best strategy.

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